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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,921	HAMSTROM ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *65-83 and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *65-83 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. After review and reconsideration, the finality of the Office action of Paper No. 13 is withdrawn.

2. Claims 65, 66, 73, 75, 77, 79, 80 and 83 have been amended. Claims 1-64 and 84-89 have been canceled. Claim 90 has been added. Claims 65-83 and 90 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 65-83 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 65, 66, 69, 7375, 77, 79, 80, 83, 90 recite "an antibody or biologically active fragment thereof derived from a first species". The metes and bounds of "derived from" are unclear. It is unclear if "derived from" reads solely on sub fragments of the original antibody, or if "derived from" encompasses other structural modifications.

It is unclear how claim 70 further limits claim 69. Claim 70 is drawn to a complex in which the binding region of the bifunctional molecule comprises fragment B of protein A. Thus the claim encompasses any fusion protein which minimally comprises fragment B and an immunoglobulin constant region. It is noted that the claim is also rejected because the metes and bounds of "derived from" are unclear. Claim 69 specifies the binding region is derived from protein A, and thus can be read as limited by full length protein A. Claim 70 encompasses a larger scope of products being limited only to fragment B of protein A, whereas claim 69 is limited by the full length protein A. If "derived from" reads only on fragments of an antibody from a first species it is unclear how claim 70 further limits claim 69, because the scope of claim 70 would encompass a larger genus of proteins than the scope of claim 69.

Claims 65, 66, 69, 73, 75, 77, 79, 80, 83, 90 recite "an antibody or biologically active fragment thereof derived from a first species". the metes and bounds of "biologically active

fragment thereof" are unclear. Antibodies possess numerous domains which confer a number of specific biological activities in vivo or in vitro. For instance, a F(ab)2 fragment directed to a cell surface receptor can have the biological activity of cross linking the receptor, a scFv antibody can have the biological activity of permeating tumor vasculature.

Claim 72 recites "a histidine rich glycoprotein". Only one histidine rich glycoprotein is recognized in the art as "the" histidine rich glycoprotein(Biochemistry, 1996, Vol. 35, pp. 1925-1934 and Biochemistry 1997, Vol. 36, pp. 6653-6662). It is unclear if claim 72 is referring to "the" histidine rich glycoprotein or a member of a genus of histidine rich glycoproteins. For purpose of examination, both alternatives will be considered. Accordingly, the term "rich" in claim 72 is a relative term which renders the claim indefinite. the specification fails to provide limitations as to the relative percentage of histidine within a protein which would qualify said protein as being histidine "rich".

5. Claims 65-68, 72-83 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to complexes comprising a bifunctional molecule comprising a binding region of non-antibody origin.

Claims 65-68, 72-83 and 90 are complexes comprising bifunctional molecules wherein said bifunctional molecule is defined as having a binding region of non-antibody origin, and wherein said bi-functional molecules bind to antibodies or to fragments of antibodies The claims encompass a genus of binding regions, with the only attribute required of said binding regions is the binding to an antibody or fragment thereof. The claims are also drawn to a genus of complexes, including complexes formed between the bifunctional molecule and the paratope of said antibodies and fragments and well as complexes formed between the bifunctional molecule and he constant region of said antibody or fragments. The limitation of the bifunctional molecule complexed with an antibody or a fragment thereof imparts neither structural or functional attributes to the binding regions, because the bi-functional molecule can bind to the

paratope of the antibody, and it is well known in the art that an antibody can be raised to any peptide, protein or polysaccharide structure. Thus, the genus of binding regions is highly variant because said genus includes any molecule which is itself of non-antibody origin, but can bind to an antibody. The genus includes numerous structural variants from the disclosed antibody binding regions as well as members of the genus which have different functions from the disclosed non-antibody binding regions. the genus would include epitopes of proteins causing antibody production in autoimmune disease, and epitopes of proteins expressed on cancer cells, and the other non-antibody binding regions, such as the human Fas antigen, as set forth in the art rejection below. The specification provides written description of bifunctional molecules comprising proteins from prokaryotes recognized to bind selectively to antibody constant regions. The specification also provides written description of mouse Fcgamma receptor, and the histidine rich glycoprotein also recognized to bind selectively to antibody constant regions, as well as binding regions encompassing epitopes of infectious agents such as dengue viruses, salmonella viruses, herpes simplex viruses. It is noted that the epitopes of the infectious disease agents would bind to the antibody paratope rather than the antibody constant region. The description of these non-antibody binding regions fails to describe the claimed genus of non-antibody binding regions, because the genus include any protein which is not part of an antibody, to which an antibody binds, and the description of protein A, G, L, Fc gamma receptor and the histidine rich glycoprotein are not representative of this variant genus that would bind to the constant region of the antibody of the first species, nor is the recitation of epitopes of infectious disease agents descriptive of the genus of non-antibody binding region which would bind to the paratope of the antibody of the first species. Further, the genus encompasses the human Fas/Fc fusion protein as complexed with anti-human Fas antibodies as exemplified in the art rejection below. The specification clearly does not provide adequate written description for the broad genus of bifunctional molecules claimed. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed bifunctional molecules.

(B) as drawn to binding regions "derived from" protein A, protein G or protein L and to constant regions "derived from" and antibody of a second species.

Claim 69 is reliant upon the identity of binding regions "derived from" protein G, A, or M. Claim 70 is dependent upon claim 69 wherein the binding region comprises fragment B of

protein A. Claims 65, 66, 73, 75, 77, 79, 80, 83 and 90 recite the limitation of a constant region "derived from" and antibody of a second species. The specification fails to provide a definition for "derived from" that would set the metes and bounds of the resulting products. Accordingly said claims have been rejected under 112, second paragraph. When given the broadest reasonably interpretation, the claims encompass derivatives of protein A, G, L and constant regions which encompass deletions, additions, and substitutions to the amino acid sequence as well as other non-protein modifications. The specification sets forth the written description of protein A, the Fc binding fragment of protein A, proteins G and L as non-antibody binding regions. The specification discloses that the substitution of His in place of Arg at position 435 in the human IgG constant region circumvents the aggregation of protein A linked to the Cgamma3 constant domain. The specification further suggests that aggregation can be reduced in the claimed bifunctional molecules by mutating cysteines associate with inter-chain disulfide bonds to serine. These modifications fail to represent the modification encompassed by the terms "derived from". One of skill in the art would conclude that applicant was not in possession of the genus of the claimed invention.

(C)As drawn to a bifunctional molecule comprising a histidine rich glycoprotein.

It is noted that claim 72 is rejected under 112, second paragraph because it is unclear if the claim encompasses a genus of histidine rich glycoproteins or the single histidine rich glycoprotein as described by Borza et al (Biochemistry, 1996, Vol. 35, pp. 1925-1934) or Gorgani et al (Biochemistry, 1997, Vol. 36, pp. 6653-6662). when given the broadest reasonable interpretation the claims can be read as drawn to a genus of histidine rich glycoproteins beyond the scope of the single histidine rich glycoprotein disclosed by Borza et al or Gorgani et al. The genus of histidine rich glycoproteins is highly variant because no structural or functional limitations have been placed on said genus, and a complex can be formed between an antibody raised against said histidine rich glycoprotein. Thus, the disclosure of a histidine rich glycoprotein a part of the claimed bifunctional molecule does not adequately describe the genus of claimed bifunctional molecules encompassed b the claim as numerous structural and functional alterations can be tolerated by said genus. One f skill in the art would reasonable conclude that applicant was not i possession of the claimed genus.

6. Claims 65-83 and 90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes formed between the Fc region of an antibody of a first species and a bifunctional molecule, wherein said bifunctional molecule comprises protein G, protein A, fragment B of protein A, protein L, the entire mouse Fc gamma receptor and the histidine rich glycoprotein as exemplified by Borza et al (Biochemistry, 1996, ibid) or Gorgani et al (Biochemistry, 1997, ibid), does not reasonably provide enablement for binding regions "derived from" protein A, protein G, protein L, fragments of the mouse Fc gamma receptor, or a genus of histidine rich glycoproteins.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims..

The specification teaches how to use the complexes comprising the bifunctional molecules comprising protein A, fragment B of protein A, protein G, protein L, the full length mouse Fcgamma receptor and the histidine rich glycoprotein described by Borza et al (Biochemistry, 1996, ibid) or Gorgani et al (Biochemistry, 1997, ibid) complexed with murine antibodies as substitutes for positive human control serum. The specification teaches that said non-antibody binding proteins bind to the constant regions of antibodies. Thus, a complex comprising the antibody of the first species (mouse) and a bifunctional molecule which bind to the antibody constant region and also comprises a human Fc receptor would have all the requirements of human positive control serum, in that the complex would have the appropriate antibody specificity (the paratope of the mouse antibody) and the Fc region of the human antibody (the constant region of the second species). The specification fails to teach how to make or use other histidine rich glycoproteins which are not the histidine rich glycoprotein disclosed by either Borza et al or Gorgani et al. The specification is not enabling for how to make the proteins "derived from" the constant region, outside of the scope of mutating cysteine residues associated with disulfide bonds to serines, and by mutating Arg to His at residue 435 of human IgG in order to avoid aggregation with protein A. The claims read on numerous additions, deletions and substitution of the constant region of the antibody of the second species, and the scope of the claims is not consistent with the scope of the enablement set forth. One of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed complexes comprising bifunctional molecules.

7. Claims 66, 67, 73 and 77 are rejected under 102(b) as being anticipated by Zanetti (US 5,583,202, cited in a previous Office Action).

Claim 66 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from first species and (ii) a bifunctional molecule, the bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or to one or more non-naturally-occurring groups provided thereon, and a constant region derived from an antibody of a second species, the constant region comprising at least one CH domain or an epitope thereof, wherein the binding region has a Kd for the antibody of the first species, or group provided thereon of less than 10-6 M. Claim 67 embodies the complex of claim 66 in which the binding region has a Kd for the antibody of the first species or group provided thereon of less than 10-8 M.

Claim 73 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species and (I) a bifunctional molecule, the bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or one or more groups provided thereon , and a constant region derived from an antibody of a second species, the constant region comprising at leas one CH domain or an epitope thereof, wherein the binding region binds to one or more groups provided on the antibody of the first species.

Claim 77 is drawn to a complex formed between (i) an antibody or biologically active fragment thereof derived from a first species and (ii) a bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or to one or more non-naturally occurring groups provided thereon, and a constant region comprising at least one CH domain or n epitope thereof wherein the constant region comprises one or more constant domain derived from a IgG antibody.

Zanetti discloses the complex formed between the engineered antibody, ylNANP, comprising the NANP epitope of plasmodium falciparum inserted into the CDR of an antibody. Zanetti discloses that the SP3-B4 antibody binds to the NANP epitope within the ylNANP antibody, thus fulfilling the specific embodiment of a complex. Zanetti does no teach the affinity of the SP3-B4 antibody for the ylNANP antibody, however affinity values of 10-8 M are within the range expected for antibody-antigen binding. The Office does not have the facilities and

resources to provide the factual evidence needed in order to establish that the ylNANP antibody of the prior art does not possess the same Kd values as the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

8. Claims 65-68, 77, 78, 81-83 and 90 are rejected under 102(b) as being anticipated by Lynch et al (US 5,620,889).

The specific embodiments of claims 66, 67 and 77 are set forth above. Claim 65 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species and (I) a bifunctional molecule, the bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or one or more groups provided thereon , and a constant region derived from an antibody of a second species, the constant region comprising at least one CH domain or an epitope thereof, wherein the binding region and the constant region are linked directly or are separated by a linker molecule. Claim 68 embodies the complex of claim 65 wherein the bifunctional molecule binds directly to the antibody derived from the first species. Claim 81 embodies the complex of claim 65 in which the antibody constant region comprises or consists of a single CH1 domain. Claim 82 embodies the complex of claim 65 in which the first species is a rat or mouse.

Claim 78 embodies the complex of claim 77 wherein the constant region comprises one or more CH3 gamma domains.

Claim 83 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species and (I) a bifunctional molecule, the bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or one or more groups provided thereon , and a constant region derived from an antibody of a second species, the constant region comprising at leas one CH domain or an epitope thereof, wherein the second species is human.

Claim 90 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species and (I) a bifunctional molecule, the bifunctional

molecule consisting of a binding region of non-antibody origin which binds to the antibody of the first species or one or more non-naturally occurring groups provided thereon , and a constant region derived from an antibody of a second species, the constant region consisting of at least one CH domain or an epitope thereof.

Lynch et al disclose human Fas ligand fused to the constant region of human IgG1 antibody (column 6, lines 55-59). Lynch et al disclose a complex comprising mouse antibodies and the human Fas-Fc fusion protein (column 7, lines 15-17), thus fulfilling the specific embodiment of an antibody of the first species, which is mouse, and a constant region which is human, satisfying the specific embodiments of claims 82 and 83. Lynch et al also satisfy the specific embodiments of claim 65 drawn to the direct attachment of the human Fas ligand and the antibody constant region. The bifunctional molecule disclosed by Lynch et al would also comprise a CH1 and a CH3 gamma domain because Lynch et al used the entire IgG1 constant region, thus the specific requirements of claim 78 are fulfilled. Lynch et al do not specifically teach Kd values for the immunofusion proteins. However, the claimed bifunctional molecules appear to be the same as the prior art Fas-Fc fusion proteins, absent a showing of unobvious differences. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

9. Claims 65-68, 77, 78, 81-83 and 90 are rejected under 103(a) as being unpatentable over Lynch et al (US 5,620,889) in view of Chang et al (US 5,723,125). The specific embodiments of claims 65, 66, 67, 68, 77, 78, 81-83 and 90 and the teachings of Lynch et al that fulfill said embodiments are set forth above. Claim 65 specifies that the binding region and the constant region are linked directly or are separated by a linker molecule of between 1 and 20 amino acids. Lynch et al teach that the binding region and constant regions of the bifunctional molecule are linked directly. Lynch et al do not teach a linker molecule of between 1 and 20 amino acids.

Chang et al teach fusion proteins comprising an immunoglobulin Fc linked through a non-immunogenic peptide to IFN-alpha. Chang et al teach that the peptide linker comprising the sequence GGSGGSGGGGSGGGGS is a T-cell immunological inactive peptide, and that insertion of this peptide between the two moiéties of a hybrid molecule avoids the creation of a new epitope caused by the joining of the two moieties (column 2, lines 34-40). Chang et al also teach that said linker increases the flexibility of the resulting fusion protein and helps overcome the possible steric hindrance exerted on the INF-alpha portion by the Fc portion, which steric hindrance could interfere with the biological activity of the fusion protein (column 2, lines 40-44). Chang et al suggest that the specific hybrid molecule described (i.e. the IFN-alpha-linker-Fc hybrid) is a model for the design and construction of other cytokine/Fc hybrids which could be made using the same techniques (column 2, lines 60-67).

It would have been prima facie obvious to join the human Fas to the human Fc constant region by means of the GGSGGSGGGGSGGGG linker. One of skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chang et al on the avoidance of neoantigenicity associated with the fusion of two moieties and on the advantages of increased flexibility afforded by the use of the linker and the resulting expectation that the non-Fc portion of the hybrid would retain biological activity as a result of the increased flexibility.

10. Claims 65-70, 77, 78 and 81 are rejected under 103(a) as being unpatentable over the abstract of Sekisui-Chem (Database Biotechds, Thomson Derwent, ISI on STN, Accession Number 1990-01279, JP 01060388, 07 March 1989) in view of Lynch et al (US 5,620,889). The specific embodiments of claims 65-68, 77 and 81 are set forth above. Claim 69 embodies the complex of claim 68 in which the binding region is derived from a protein selected from the group consisting of protein G, protein A and protein L. Claim 70 embodies the complex of claim 69 wherein the bind region comprises protein A. Claim 77 embodies the complex of claim 77 wherein the constant region comprises one or more CH3gamma domains.

The abstract of Sekisui-Chem teaches a bifunctional molecule comprising protein A linked via a relatively short linker peptide to the Fc region of IgG, thus fulfilling the specific embodiments of claims 77 and 78 directed to a constant domain derived from an IgG antibody

and the CH3 gamma domain which would be inherently comprised within the full length IgG constant region. The abstract of Sekisui-Chem teaches that amino acids having functional groups can be attached to the amino or carboxyl terminus of the fusion protein in order to facilitate attachment to solid supports. The abstract of Sekisui-Chem teaches that protein a can be used as an immunogenic adsorbent for diagnosis. The abstract of Sekisui-Chem does not specifically state that the protein A/Fc fusion protein is linked to a solid support to bind immunoglobulins.

Lynch et al teach that the soluble human Fas-Fc fusion protein was purified by a procedure that involved the binding of the fusion protein to protein G in an affinity column (column 7, lines 1-3).

It would have been prima facie obvious to link the Fc region of the bifunctional molecule taught by Sekisui-Chem to protein G on a solid support in order to capture antibodies which bind to protein A. One of skill in the art would be motivated with a reasonable expectation of success b the teachings of Lynch et al on the construction of an affinity support comprising a human Fas-Fc fusion protein linked to protein G on said solid support.

11. Claims 65-70 and 75-79 are unpatentable over Sekisui-Chem and Lynch et al as applied to claims 65-70, 77, 78 and 81 above, and in further view of Spooner et al (Human Pathology, 1994, Vol. 25, pp. 606-614, IDS reference) and Ozkan (US 4,681,782) and Harris et al (US 5,096,670) and Paul (Fundamental Immunology (text), 1993, pp. 296-302). The combination of Sekisui-Chem (JP 01060388) and Lynch et al (US 5,620,889) render obvious the specific embodiments of claims 65-70, 77, 78 and 81 for the reasons set forth above. Neither Sekisui-Chem nor Lynch et al teach a bifunctional molecule comprising a constant region derived from a IgM or an IgA antibody.

Spooner et al teach that for many applications it is usual to incorporate a an amplification step or several amplification steps, so that strong signals can be generated from the binding of small amounts of reagents (page 610, second column lines 18-21).

Ozkan teaches that the determination of the class of the antibody component or a circulating immune complex sheds light on both the origins of the disease and the prognosis of the disease (column 1, lines 59-68).

Harris et al teach the use of a positive control comprising human serum to establish an maximum value for detection (column 9, lines 22-26)

Paul teaches the CH domains of IgM antibodies and IgA antibodies (pages 300-302, under the heading of "Fc regions").

Zeltzer and Seeger (Journal of Imunological Methods, 1977, Vol. 17, pp. 163-175) teach that protein A binds to IgG subclasses and is useful for the detection of bound antibodies and antibodies in human sera (page 172, lines 15-18) and that radiolabeled protein A is a more sensitive reagent than a radiolabeled antibody for the detection of cell bound antibodies (page 172-173, bridging sentence).

It would be prima facie obvious to one of skill in the art at the time the invention was made to recombinantly produce protein A fused to the constant domains of IgM and/or IgA. One of skill in the art would be motivated to make these reagents for binding to antibodies via protein A in order to have available a variety of agents which could substitute for the positive control comprising human serum to establish a maximum value for the detection of an antibody of a specific class as taught by Harris et al.

12. Claims 65-70 and 75-79 are unpatentable over the abstract of Sekisui-Chem and Lynch et al as applied to claims 65-70, 77, 78 and 81 in section 10, above, and in further view of Bjorck et al (US 4,876,194) and Frame et al (US 5,665,558). The combination of Sekisui-Chem (JP 01060388) and Lynch et al (US 5,620,889) render obvious the specific embodiments of claims 65-70, 77, 78 and 81 for the reasons set forth above. Neither Sekisui-Chem nor Lynch et al teach complex comprising a fusion protein, wherein said fusion protein comprises protein L or protein G linked directly or separated by a linker from a constant region comprising a CH domain.

Frame et al teach that protein G binds to the Fc domain mammalian IgG immunoglobulins (column 4, lines 21-22). Frame et al teach that protein G does not bind to IgM, IgA and IgD (column 4, lines 18-19). Frame et al additionally teach an engineered protein comprising four Fc binding domains from Protein A and two Fc binding domains from Protein G which binds to all human IgG subclasses in addition to IgA, IgE, IgM and IgD.

Bjorck et al teach that protein L, in contrast to proteins A and G, binds only to Ig kappa and lambda light chains, and that protein L can therefore be used as a general binding substance for all Ig classes (column 1, lines 26-36).

It would be prima facie obvious to one of skill in the art at the time the invention was made to make fusion proteins comprising protein G, protein A/G or protein L substituted for protein A in the fusion protein taught by the abstract of Sekisui-Chem. One of skill in the art would be motivated to do so by the teachings of Frame et al on specificity of the reaction of protein G or protein A with the Fc portion of immunoglobulins and the teachings of Bjorck et al on the use of protein L as a general reagent for binding to immunoglobulins of all classes. One of skill in the art would be motivated to use the resulting fusion proteins as positive controls in order to ascertain the level of total immunoglobulin in a sample versus specific immunoglobulin classes, such as IgG.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308 8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308 3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
12/29/03